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10/771,440	02/05/2004	Michal Daniely	26003	3178

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EXAMINER	
DUFFY, BRADLEY	

ART UNIT	PAPER NUMBER
1643	

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03/20/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/771,440	DANIELY ET AL.	
	Examiner	Art Unit	
	BRADLEY DUFFY	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 November 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *37,39,40,54,55,57 and 72-81* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *37,39,40,54,55,57 and 72-81* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *05 February 2004* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Exhibit A and B*.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on November 8, 2007, has been entered.

1. The amendment filed November 8, 2007, is acknowledged and has been entered. Claims 1-36, 38, 41-53, 56 and 58-71 have been canceled. Claims 37, 54, 55, 72 and 73 have been amended. Claims 74-81 have been newly added.

2. Claims 37, 39, 40, 54, 55, 57 and 72-81 are pending in the application and are under examination.

Priority

3. Applicant's claim under 35 USC §§ 119 and/or 120 for benefit of the earlier filing date of the U.S. Provisional Application No. 60/459,992, filed April 4, 2003, is acknowledged.

In the response filed November 8, 2007, at page 7, Applicant appears to be arguing that removing the language "at least two stains" establishes priority to US Provisional Application 60/459,992.

In reponse, claims 37, 39, 40, 54, 55, 57 and 72-81 still do not properly benefit under §§ 119 and/or 120 by the earlier filing date of the priority document claimed, since the claims are rejected under 35 U.S.C. § 112, first paragraph, as lacking adequate written description and/or a sufficiently enabling disclosure.

To receive benefit of the earlier filing date under §§ 119 and/or 120, the later-filed application must be an application for a patent for an invention which is

also disclosed in the prior application (the parent or original nonprovisional application or provisional application); the disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994). See M.P.E.P. § 201.11.

Accordingly, the effective filing date of the claims is deemed the filing date of the instant application, namely February 5, 2004.

Grounds of Objection and Rejection Withdrawn

4. Unless specifically reiterated below, Applicant's amendment and/or arguments filed November 8, 2007, have obviated or rendered moot the grounds of rejection set forth in the previous Office action mailed August 10, 2007.

Response to the Declaration under 37 C.F.R. § 1.132

5. The declaration under 37 C.F.R. § 1.132 filed November 8, 2007 is sufficient to overcome the rejection of the claims under 35 U.S.C. 102(a) as being anticipated by Daniely et al (Annales de Genetique, 46:153, September 2003), as evidenced by Shimoni et al. [Leukemia, 16:1413-1418, August 2002), Skacel et al. (Anal. Quant. Cytol. Histol. 23(6): 381-387, December 2001], and the rejection of the claims under 35 U.S.C. 103(a) as being unpatentable over Daniely et al. (Annals de Genetique, 46:153, September 2003) in view of US Patent 6,418,236 (Ellis et al., July 9, 2002), as set forth in the last Office action, for the following reasons:

In this case, the declaration states:

> We, Michal Daniely of 5 Harimon Street, 55900 Genei Tikva, Israel; Tal Kaplan of 4/3 HaMagal Street, 70800 Gan-Yavne, Israel; Eran Kaplan of 3 Paldi Street, 76248 Rechovot, Israel; and Avner Freiberger of 19b Emek Dotan Street, 44621 Kfar-Saba, Israel; declare as follows:
>
> 1. We are the only inventors of the invention disclosed and claimed in the above-ideatified application; and

> 2. That the co-authors, Ronni Rona, Shirtey Olsfanger, Lea Elboim, Yulia Zilbersteia, Dvora Kidron, Sylvia Lew and Iian Leibovich identified in an abstract entitled "Combined analysis of morphology and FISH for the monitoring of bladder cancer", published on September 2003 in Annales de Genetique, 46:153, were identified as co-authors on an oral presentation for their collaborative efforts operating under our guidance and direction, and were not co-inventors of the above identified application.

Accordingly, Applicant's declaration under 37 C.F.R. § 1.132 filed November 8, 2007 establishes that co-authors Ronni Rona, Shirtey Olsfanger, Lea Elboim, Yulia Zilbersteia, Dvora Kidron, Sylvia Lew and Iian Leibovich of the abstract published in Annales de Genetique (46:153, September 2003), were not co-inventors of US Application 10/771,440 and that inventors Michal Daniely, Tal Kaplan, Eran Kaplan and Avner Freiberger were the only inventors of the claimed invention. Therefore, the declaration is sufficient to establish that the abstract entitled "Combined analysis of morphology and FISH for the monitoring of bladder cancer", published on September 2003 in Annales de Genetique, 46:153 is not “by others” and therefore, this publication is not available as prior art under 35 U.S.C. 102(a).

Furthermore, in reviewing the declaration under 37 C.F.R. § 1.132 filed November 8, 2007, the Examiner has subsequently determined that the oral presentation of the Daniely et al reference (of record) at the FECC conference in September 2003 occurred in Italy (see attached Exhibit A). Accordingly, as there is no evidence that the methods disclosed in the Daniely et al oral presentation at the FECC conference in September 2003 were known or used by others in this *country* (see 35 U.S.C. 102 (a)),the oral disclosure of these methods is not available as prior art.

Grounds of Rejection Maintained

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. The rejection of claims 37, 39, 40, 55, 57 and 72-81 are under 35 U.S.C. 102(b), as being anticipated by Skacel et al (of record), is maintained.

At page 10 of the amendment filed November 8, 2007, Applicant has traversed this ground of rejection.

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

Applicant appears to be arguing that Skacel et al do not anticipate the claims because Skacel et al do not mention methods to stain cells with a May-Grunwald-Giemsa stain, a Giemsa stain, a Papanicolau stain or a Hematoxylin-Eosin stain and methods to stain the cells by FISH.

In response, the Examiner notes that Skacel et al does teach staining the same malignant transitional carcinoma cells with Papanicolaou stain and FISH probes specific to chromosomes 3, 7, 17 and 9p21[1] (see entire document, e.g., page 383, Figure 2 legend, page 384 and page 386). Accordingly, Skacel et al teach processes that are materially and manipulatively indistinguishable from the claimed process and therefore, absent a showing of any difference, the process disclosed by the prior art is deemed the same as the claimed process.

For these reasons, after careful and complete consideration, the Examiner disagrees with Applicant's contention that the rejection has been overcome and

[1] The FISH probes disclosed by Skacel et al appear to be species of the probes recited in newly added claims 74-81

the rejection of claims 37, 39, 40, 55, 57 and 72-81 under 35 U.S.C. 102(b) as being anticipated by Skacel et al (of record) is maintained.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

9. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. The rejection of claims 37 and 54 under 35 U.S.C. 103(a) as being unpatentable over Skacel et al (of record) in view of US Patent No. 6,418,236 (of record), is maintained.

At page 11 of the amendment filed November 8, 2007, Applicant has traversed this ground of rejection.

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

Applicant has reiterated that Skacel et al pertains to methods of staining cells with DAPI stain and FISH probes and do not mention methods to stain cells with a May-Grunwald-Giemsa stain, a Giemsa stain, a Papanicolau stain or a Hematoxylin-Eosin stain and appears to be further argued that US Patent No. 6,418,236 only pertains to an automated cell imaging device capable of dual imaging that images cells stained by only one stain from different tissue sections. Therefore, Applicant concludes on page 12 that the combination of Skacel et al and US Patent No. 6,418,236 "could not anticipate a method of identifying transitional cell carcinoma or diagnosing bladder cancer by staining the same nucleated cells with May-Grunwald-Giemsa, Giemsa, Papanicolau or Hematoxylin-Eosin and FISH as now claimed".

In response, this is not found persuasive, because as explained in the above rejection of the claims under 35 U.S.C. 102(b), Skacel et al teach methods of identifying transitional cell carcinoma cells and methods of diagnosing bladder cancer by staining the same cells with a Papincolau stain and FISH probes. The deficiency of Skacel is that it does not expressly teach imaging the cells with an automated imaging device capable of dual imaging. Notably, this deficiency is made up for in the teachings of US Patent No. 6,418,236, because as explained in the previous office action at page 15, the parallel imaging technique of tissue sections is only disclosed as one particular embodiment of using the automated cell imaging device capable of at least dual imaging in US Patent 6,418,236 at column 1, line 65. At column 1, lines 56-59, US Patent 6,418,236 discloses that the microscope is capable of dual imaging to determine if the same cells are

stained with two stains of interest. Furthermore at column 2, lines 27-31 US Patent 6,418,236 discloses that each sample "is processed with a stain, counterstain, immunohistochemical technique, in situ hybridization technique, or a *combination*[2] thereof. Each sample is then scanned and an image is obtained from each of the samples".

Therefore, the examiner maintains that it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to identify transitional cell carcinoma cells or diagnose bladder cancer from a urine sample, by staining nucleated cells of a urine sample by the methods of Skacel et al and imaging the same stained cells with the automated microscope capable of dual imaging as taught by US Patent 6,418,236 to identify transitional cell carcinoma cells or diagnose bladder cancer. Notably, there is an advantage and reasonable expectation of success in practicing such methods because as set forth in the Office action mailed 12/27/2006 at page 15 "automated imaging analysis "eliminates the need for operator input to locate biological objects or areas of interest for analysis" as taught by US Patent 6,418,236 (see column 8, lines 30-32)" and because the imaging device taught by US Patent 6,418,236 is capable of dual imaging of the same cells on the same sample.

For these reasons, after careful and complete consideration the Examiner disagrees with Applicant's contention that Applicant's claim amendments, arguments and remarks have overcome this rejection and the rejection of claims 37 and 54 under 35 U.S.C. 103(a) as being unpatentable over Skacel et al in view of US Patent No. 6,418,236 is maintained.

New Grounds of Objection

Drawings

11. The drawings are objected to because the specification discloses that Figures 1-4 are color drawings or photographs (see pages 7-8 of the

[2] Emphasis added

specification) and a petition under 37 CFR 1.84(a)(2) has not been filed to accept color drawings or photographs in this case.

Color photographs and color drawings are not accepted unless a petition filed under 37 CFR 1.84(a)(2) is granted. Any such petition must be accompanied by the appropriate fee set forth in 37 CFR 1.17(h), three sets of color drawings or color photographs, as appropriate, and, unless already present, an amendment to include the following language as the first paragraph of the brief description of the drawings section of the specification:

> The patent or application file contains at least one drawing executed in color. Copies of this patent or patent application publication with color drawing(s) will be provided by the Office upon request and payment of the necessary fee.

The color drawings or photographs must be of sufficient quality such that all details in the drawings are reproducible in black and white in the printed patent. Color photographs will be accepted if the conditions for accepting color drawings and black and white photographs have been satisfied. See 37 CFR 1.84(b)(2).

Specification

12. The disclosure is objected to because of the following informalities:

a. The specification is objected to because the use of improperly demarcated trademarks has been noted in this application. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner that might adversely affect their validity as trademarks. See MPEP § 608.01(v).

An example of such an improperly demarcated trademark appearing in the specification is UroVysion® (see numerous instances, e.g., page 17, line 11).

Appropriate correction is required. Each letter of a trademark should be capitalized or otherwise the trademark should be demarcated with the appropriate symbol indicating its proprietary nature (e.g., ™, ®), and accompanied by generic terminology. Applicants may identify trademarks using the "Trademark" search engine under "USPTO Search Collections" on the

Internet at <http://www.uspto.gov/web/menu/search.html>.

b. The specification is objected to as it does not include the following language as the first paragraph of the brief description of the drawings section of the specification:

> The patent or application file contains at least one drawing executed in color. Copies of this patent or patent application publication with color drawing(s) will be provided by the Office upon request and payment of the necessary fee.

In this case, Figures 1-4 are a color drawings or photographs. Accordingly, a petition under 37 CFR 1.84(a)(2) to accept color drawings needs to be filed and the specification needs to be amended with the proper language. See 37 CFR § 1.84.

c. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Appropriate correction is required.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

13. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

14. Claims 37, 39, 40, 54, 55, 57 and 72-81 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

(a) Claims 37, 39, 40, 54, 55, 57 and 72-81 are indefinite because claims 37, 55, 72 and 73 recite staining cells “by May-Grünwald-Giemsa, Giemsa, Papanicolau or Hematoxylin-Eosin”. This recitation renders the claims indefinite because the recited elements “May-Grünwald-Giemsa, Giemsa, Papanicolau or

Hematoxylin-Eosin" are biological stains that are known to be used in multiple staining methods and are not staining methods, per se. Accordingly, the claims merely provide for the use of these stains, but, since the claims do not set forth any steps involved in the staining process, it is unclear what process applicant is intending to encompass, because it cannot be ascertained how those "stains" are to be used. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced. Accordingly, it is submitted that staining nucleated cells of the urine sample "by" one of stains does not particularly identify the process step set forth in the claims to stain the nucleated cells of the urine sample. Moreover, if, on the other hand, the recited elements "May-Grünwald-Giemsa, Giemsa, Papanicolau or Hematoxylin-Eosin" are intended to identify staining processes, which are so designated, which staining techniques and which particular stains are those? Without knowing the process steps that must be used to stain nucleated cells of the urine sample in practicing the claimed invention, the claims cannot be construed unambiguously. Thus, the claims fail to delineate the subject matter that Applicant regards as the invention with the requisite degree of clarity and particularity to permit the skilled artisan to know or determine infringing and non-infringing subject matter and thereby satisfy the requirement set forth under 35 U.S.C. § 112, second paragraph.

(b) Claims 37, 39, 40, 54, 55, 57 and 72-81 are also indefinite because claims 37, 55, 72 and 73 are directed to a methods of identifying transitional cell carcinoma cells in a urine sample or methods of diagnosing bladder cancer; yet the claims merely recite process steps to stain nucleated cells of the urine sample and image the stained cells. How does practicing these process steps identify transitional cell carcinoma cells or determine the presence or absence of cancerous cells in the urine? There is no process step that clearly relates back to the purpose or objective of the claimed invention; consequently, the skilled artisan could not determine whether each and every process step considered essential to the practice of the claimed invention has been included in the body of

the claim. Notably, since the claims lack any active process step that sets forth how to identify transitional cell carcinoma cell or determine the presence or absence of cancerous cells the claims appear to be incomplete for omitting essential steps to achieve the claimed objective. Thus, in the absence of an active process step positively setting forth how the method objective is achieved, as recited in the preamble, the claims fail to delineate the subject matter that Applicant regards as the invention with the requisite degree of clarity and particularity to permit the skilled artisan to know or determine infringing and non-infringing subject matter and thereby satisfy the requirement set forth under 35 U.S.C. § 112, second paragraph.

(c) Claims 74-81 are further indefinite for reciting "said FISH is effected using a FISH probe". Notably, the term "effect" is defined in the relevant art, for example, by Stedman's Online Medical Dictionary, 27th Edition as meaning: "The result or consequence of an action" (see Exhibit B) (Copyright © 2007 Lippincott Williams & Wilkins). Given this definition of effect, one of skill in the art would reasonably conclude that the claims merely provide for the use of FISH probes, without setting forth any steps involved in the process that would allow one of skill in the art to determine how these FISH probes are used to *effect* FISH. How (or when) do the recited FISH probes effect FISH? Accordingly, it is unclear what process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced. Thus, the claims fail to delineate the subject matter that Applicant regards as the invention with the requisite degree of clarity and particularity to permit the skilled artisan to know or determine infringing and non-infringing subject matter and thereby satisfy the requirement set forth under 35 U.S.C. § 112, second paragraph.

15. Claims 37, 39, 40, 54, 55, 57 and 72-81 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in

such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This is a “written description” rejection.

The considerations that are made in determining whether a claimed invention is supported by an adequate written description are outlined by the published Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, para. 1, ``Written Description'' Requirement (Federal Register; Vol. 66, No. 4, January 5, 2001). A copy of this publication can be viewed or acquired on the Internet at the following address: <http://www.gpoaccess.gov/>.

Claims 37, 39, 40, 54, 55, 57 and 72-81 are directed to methods of identifying transitional cell carcinoma cells in a urine sample and to methods of diagnosing bladder cancer in a subject comprising: staining nucleated cells of the urine sample by “May-Grünwald-Giemsa, Giemsa, Papanicolau or Hematoxylin-Eosin” to thereby obtain stained nucleated ceils, staining said stained nucleated cells by FISH and imaging said stained nucleated cells to thereby identify the transitional cell carcinoma cells in the urine sample or to thereby determine the presence or absence of cancerous cells within said stained nucleated cells, wherein presence of said cancerous cells is indicative of a positive cancer diagnosis, respectively. Claims 74-81 further recite that said FISH is effected using a structurally and functionally diverse genus of “FISH probes to a pericentromeric region of chromosomes 3, 7 and 17”.

Notably, as explained in the above rejection of the claims under 35 U.S.C. 112, second paragraph, the claims lack any active process step that sets forth how to identify transitional cell carcinoma cells or determine the presence or absence of cancerous cells by using a process comprising the claimed staining and imaging methods; and therefore, it is apparent that one of skill in the art could not immediately envision or determine which further process steps are necessary to identify transitional cell carcinoma cells in urine samples or determine the presence or absence of cancerous cells in urine samples.

In this case, it is submitted that the specification does not adequately describe the claimed invention because those of skill in the art recognize that methods of identifying cancerous cells or diagnosing cancer in a subject require a correlative step that determines whether or not a biomarker of the cancer identifies the cancer cells in a biological sample. For example, Tockman et al (Cancer Res, 52:2711s-2718s, 1992) teach that methods of using biomarkers for cancer diagnosis require that many highly unpredictable considerations be validated and correlated to determine the biomarkers effectiveness (see entire document, e.g., pages 2714s and 2716s). Although the reference is drawn to biomarkers for early lung cancer detection, the basic principles taught are clearly applicable to other oncogenic disorders. Tockman et al teach that prior to the successful application of cancer biomarkers, research must validate the markers against acknowledged disease end points, establish quantitative criteria for marker presence/absence and confirm marker predictive value in prospective population trials (see abstract). The reference further teaches that once selected, the sensitivity and specificity of the biomarker must be validated to a known (histology/cytology-confirmed) cancer outcome (p. 2714s, see Biomarker Validation against Acknowledged Disease End Points). Accordingly, it is apparent that methods to identify transitional cell carcinoma cells in a urine sample or methods to determine the presence or absence of cancerous cells in a urine sample, require an active process step to measure and determine whether established biomarkers of bladder cancer are present in the cells compared to normal bladder epithelial cells to identify them as transitional cell carcinoma cells. Notably, the instant claims do not set forth a process step that identifies how the claimed process identifies bladder cancer biomarkers that would be able to identify transitional cell carcinoma cells in a urine sample or how the claimed process diagnoses bladder cancer in a subject. Accordingly, one of skill in the art would not immediately envision or recognize that Applicant was in possession of the claimed methods to identify transitional cell carcinoma cells in a urine sample or methods to diagnose bladder cancer unless the claims recite an active

process step that sets forth how the recited staining and imaging steps achieve the method objectives.

Secondly, where the claims are drawn to staining nucleated cells of the urine sample by "May-Grünwald-Giemsa, Giemsa, Papanicolau or Hematoxylin-Eosin", as explained in the above rejection of the claims under 35 U.S.C. 112, second paragraph, these terms are commonly used to describe biological stains and are not staining methods, per se. Accordingly, it is submitted that one of skill in the art could not immediately envision or recognize the staining methods being referred to in the claims.

Finally, where the claims are directed to effecting FISH using a structurally and functionally diverse genus of "FISH probes to a pericentromeric region of chromosomes 3, 7 and 17", it is submitted that the specification does not adequately describe the genus of FISH probes to which the claims are directed because there is no correlation of any particular identifying structural feature of these probes, which is shared by members of the genus, and any particular identifying function that is also shared by at least a substantial number of those probes. As evidenced by Horvath et al, (Gen. Res., 10:839-852, 2000), for example, "The pericentromeric regions of human chromosomes pose particular problems for both mapping and sequencing. These difficulties are due, in large part, to the presence of duplicated genomic segments that a distributed among multiple human chromosomes." Accordingly, it is apparent that FISH probes to a pericentromeric region of chromosomes 3, 7 and 17 are a structurally diverse and functionally diverse genus of probes, some of which are specific for chromosomes 3, 7 and 17 and some of which recognize multiple different chromosomes. However, the specification only adequately describes transitional cell carcinoma cells in urine samples with polyploidy for chromosomes 3, 7 and 17 (See e.g., pages 7 and 8, description of Figure 1 and page 28). Accordingly, without knowing the sequences of the pericentromeric regions of the human chromosomes and the sequences of the FISH probes to a pericentromeric region of chromosomes 3, 7 and 17, one of skill in the art could

not immediately envision, recognize or predict which of those probes are specific for chromosomes 3, 7 and 17 and could be used in methods to determine if cells in a urine sample are polyploid for chromosomes 3, 7 and 17 from those that could not.

Thus, the specification fails to adequately describe the genus of "FISH probes to a pericentromeric region of chromosomes 3, 7 and 17", as a whole, because the skilled artisan could not immediately envision, recognize or distinguish as least most of its members from other FISH probes to a pericentromeric region of chromosomes, as the specification fails to describe its members as sharing any particularly identifying (i.e., substantial) structural feature, which correlates with any one particularly identifying functional feature that is also shared by many, if not all, of these FISH probes to a pericentromeric region of chromosomes; and therefore the specification would not reasonably convey to the skilled artisan that Applicant had possession of the claimed invention at the time the application was filed.

16. Claims 37, 39, 40, 54, 55, 57 and 72-81 are rejected under 35 U.S.C. 112, first paragraph, because the specification, **while being enabling for using** methods encompassed by the claims, which are taught in the prior art, **does not reasonably provide enablement for making and using** the claimed methods. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

MPEP § 2164.01 states:

> The standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of *Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916) which postured the question: is the experimentation needed to practice the invention undue or unreasonable? That standard is still the one to be applied. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Accordingly, even though the statute does not use the term "undue experimentation," it has been interpreted to require that the claimed invention be enabled so that any person skilled in the art can make and use the invention without undue experimentation. *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". These factors, which have been outlined in the Federal Circuit decision of *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), include, but are not limited to, the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed. See also *Ex parte Forman*, 230 USPQ 546 (BPAI 1986).

The amount of guidance, direction, and exemplification disclosed in the specification, as filed, would not be sufficient to enable the skilled artisan to make and/or use the claimed invention at the time the application was filed without undue and/or unreasonable experimentation.

As explained in the above rejection of the claims, as failing to comply with the written description requirement, the claims are directed to methods of identifying transitional cell carcinoma cells in a urine sample and to methods of diagnosing bladder cancer in a subject comprising: staining nucleated cells of the urine sample by May-Grünwald-Giemsa, Giemsa, Papanicolau or Hematoxylin-Eosin to thereby obtain stained nucleated ceils, staining said stained nucleated cells by FISH and imaging said stained nucleated cells to thereby identify the transitional cell carcinoma cells in the urine sample or to thereby determine the presence or absence of cancerous cells within said stained nucleated cells, wherein presence of said cancerous cells is indicative of a positive cancer diagnosis, respectively. However, the specification does not provide any specific, non-general guidance as to how to identify transitional cell carcinoma cells in a urine sample or diagnose bladder cancer in a subject using the process steps recites in the claimed methods.

Notably, as evidenced by the teachings of Tockman et al (Cancer Res,

52:2711s-2718s, 1992), methods of to identify transitional cell carcinoma cells in a urine sample or methods to determine the presence or absence of cancerous cells in a urine sample would require an active process step to measure and determine whether established biomarkers of bladder cancer are present in the cells compared to normal bladder cells at levels which identify them as transitional cell carcinoma cells. Notably, the instant claims do not set forth a process step that identifies how the claimed process identifies bladder cancer biomarkers which would be able to identify transitional cell carcinoma cells in a urine sample or how the claimed process diagnoses bladder cancer in a subject. Accordingly, one of skill in the art would be subject to undue and unreasonable experimentation to use the claimed methods to identify transitional cell carcinoma cells in a urine sample or to diagnose bladder cancer because staining the cells and imaging the cells as claimed could not be used to achieve the claimed objective. In the absence of a correlative step that sets forth a process to identify biomarkers associated with transitional cell carcinoma cells as compared to normal bladder epithelial cells, one of skill in the art could not identify transitional cells carcinoma cells and therefore, would be subject to undue and unreasonable experimentation. Notably, while the specification teaches that, e.g., transitional cell carcinoma cells have a high nucleus to cytoplasm ratio as well as gains of chromosomes 3, 7 and 17 as compared normal bladder epithelial cells, the claims do not require such a determination therefore, one of skill in the art would be subject to undue experimentation to use the claimed invention.

Applicant is reminded that reasonable correlation must exist between the scope of the claims and scope of enablement set forth.

In deciding *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970), the Court indicated the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. "Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of

the public to understand and carry out the invention." *Genentech Inc. v. Novo Nordisk A/S*, 42 USPQ2d 1001, 1005 (CA FC 1997).

In conclusion, upon careful consideration of the factors used to determine whether undue experimentation is required, in accordance with the Federal Circuit decision of *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the amount of guidance, direction, and exemplification disclosed in the specification, as filed, is not deemed sufficient to have enable the skilled artisan to make and/or use the claimed invention at the time the application was filed without undue and/or unreasonable experimentation.

Conclusion

17. No claim is allowed.

18. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Hailing et al (of record) discloses a method of identifying transitional cell carcinoma cells and diagnosing bladder cancer in cells stained with FISH stains. Bubendorf et al (of record) discloses a method of identifying transitional cell carcinoma cells and diagnosing bladder cancer in cells stained with standard Papanicolaou stain or FISH stains. Darzynkiewicz et al (of record) discloses an automated cell-imaging device capable of dual imaging. Shimoni et al (of record) discloses an automated cell-imaging device capable of dual imaging of cells stained with a May-Grunwald-Giemsa stain and FISH probes. Boon et al (J. Clin. Path., 34:612-615, 1981) discloses a method of identifying transitional cell carcinoma cells and diagnosing bladder cancer in cells stained with a Giemsa stain or a Papanicolaou stain. Otto et al (A. J. Path., 150(6):1919-1923, 1997) discloses a method of identifying transitional cell carcinoma cells and diagnosing bladder cancer in cells stained with a Hematoxylin stain and an Eosin stain.

19. Any inquiry concerning this communication or earlier communications from

the examiner should be directed to Brad Duffy whose telephone number is (571) 272-9935. The examiner can normally be reached on Monday through Friday 7:00 AM to 4:30 PM with alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Respectfully,
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/Stephen L. Rawlings/

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